View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Osteoarthritis and Cartilage 23 (2015) 851–859

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Diabetes is a risk factor for knee osteoarthritis progression

F. Eymard † [a], C. Parsons ‡ [a], M.H. Edwards ‡, F. Petit-Dop §, J.-Y. Reginster ‖, O. Bruyère ‖, P. Richette ¶, C. Cooper ‡ [b], X. Chevalier † * [b]

† Department of Rheumatology, AP-HP Henri Mondor Hospital, F-94010 Créteil Cedex, France
‡ MRC Lifecourse Epidemiology Unit, Southampton General Hospital, SO16 6YD Southampton, UK
§ Clinical Department, Servier Laboratory, 92150 Suresnes, France
‖ Department of Public Health and Health Economics, University of Liege, 4020 Liege, Belgium
¶ Department of Rheumatology, AP-HP Lariboisière Hospital, F-75475 Paris Cedex 10, France

ARTICLE INFO

Article history:
Received 13 October 2014
Accepted 23 January 2015

Keywords:
Knee osteoarthritis
Radiological progression
Metabolic syndrome
Diabetes
Obesity

SUMMARY

Purpose: Recent studies have suggested that metabolic factors (obesity, diabetes, hypertension and dyslipidemia) and their clustering in metabolic syndrome (MetS) might be involved in the pathophysiology of knee osteoarthritis (OA). We investigated their impact on radiographic progression by an annualised measure of the joint space narrowing (JSN) of the medial tibiofemoral compartment.
Methods: 559 patients older than 50 years with symptomatic knee OA were recruited for the placebo arm of the SEKOIA trial. The presence of diabetes, hypertension and dyslipidemia was determined at baseline interview. Body mass index (BMI) was calculated, obesity was considered >30 kg/m^2. MetS was defined by the sum of metabolic factors ≥3. Minimal medial tibiofemoral joint space on plain radiographs was measured by an automated method at baseline and then annually for up to 3 years.
Results: The mean age of patients was 62.8 [62.2–63.4] years; 392 were women. A total of 43.8% was obese, 6.6% had type 2 diabetes, 45.1% hypertension, 27.6% dyslipidemia and 13.6% MetS. Mean annualised JSN was greater for patients with type 2 diabetes than without diabetes (0.26 [−0.35 to −0.17] vs 0.14 [−0.16 to −0.12] mm; $P = 0.001$). This association remained significant after adjustment for sex, age, BMI, hypertension and dyslipidemia ($P = 0.018$). In subgroup analysis, type 2 diabetes was a significant predictor of JSN in males but not females. The other metabolic factors and MetS were not associated with annualised JSN.
Conclusion: Type 2 diabetes was a predictor of joint space reduction in men with established knee OA. No relationships were found between MetS or other metabolic factors and radiographic progression.
© 2015 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Introduction

Knee osteoarthritis (OA) is the most common joint disease[1] and a major source of disability[2,3]. Risk factors of knee OA are age, female gender, heritability, misalignment, tears of the central pivot ligaments and/or menisci, muscle weakness and obesity[4–8]. The association of obesity and knee OA was primarily explained by mechanical overloading on the cartilage. Nonetheless, evidence for an association of overweight and OA lesions in non-weight-bearing joints such as digital interphalangeal joints (Risk Ratio = 1.9) has highlighted the contribution of a systemic pathway[9]. Moreover, a recent study showed that the addition of cardiometabolic clustering to obesity had a cumulative effect on knee OA prevalence in women[10] while several former cross-sectional studies had already reported an association between OA and hypertension[11], dyslipidemia[12,13], and hyperglycemia[13,14].

Clustering of these factors in the so-called metabolic syndrome (MetS)[15–18] is considered an archetype of chronic low-grade inflammation, especially involved in atherosclerosis disease[19–21]. This low-grade systemic inflammation may also contribute to the pathophysiology of OA[22,23] and several studies attempted to confirm this hypothesis. Transversal studies evaluating the link between MetS and knee OA yielded conflicting results[24–27]. However, two recent longitudinal studies demonstrated a strong cumulative effect of metabolic factors on early-[28] or end-stage[29] knee OA incidence. Moreover, type 2 diabetes was recently found an

* Address correspondence and reprint requests to: X. Chevalier, Department of Rheumatology, AP-HP Henri Mondor Hospital, F-94010 Créteil Cedex, France.
E-mail address: xavier.chevalier@hmn.aphp.fr (X. Chevalier).
[a] The authors Eymard and Parsons contributed equally to the work.
[b] The authors Cooper and Chevalier contributed equally to the work.

http://dx.doi.org/10.1016/j.joca.2015.01.013
1063-4584/© 2015 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

independent risk factor of severe OA with a Hazard Ratio (HR) of 2.1 ($P = 0.023$) after adjustment for body mass index (BMI)[30].

Yoshimura *et al.* first evaluated the impact of metabolic factors on radiographic progression of knee osteoarthritic lesions over 3 years[28]. They showed that obesity and hypertension were independent risk factors for radiographic progression and that accumulation of each metabolic factor was also associated with progression[28]. Nonetheless, this study did not strictly assess OA disease progression because authors also included patients without knee OA (KL grade < 2) at baseline. Moreover, they defined radiographic progression as a worsening of KL grade[31], which is weakly sensitive to small changes[32]. An accurate approach to radiographic progression can only be obtained by strict radiographic measurement of joint space width (JSW), and this evaluation is still accepted as the gold standard in any chondroprotective trials[33].

The SEKOIA trial provided a unique opportunity to study the involvement of metabolic factors in disease progression with an accurate semi-automatic measurement of JSW in patients with symptomatic knee OA. The main purpose of this study was to assess the involvement of each metabolic factor (obesity, diabetes, hypertension, dyslipidemia) and of their clustering in MetS on knee OA progression. Secondary endpoints included the evaluation of an association of ischemic disease and knee OA progression and the impact of metabolic factors on pain and function in knee OA.

Material and methods

Characteristics of SEKOIA study

SEKOIA was a randomised, double blind, placebo-controlled phase 3 trial of outpatients with symptomatic knee OA performed in 98 centres in 18 countries. This 3-year study compared the effectiveness of strontium ranelate (1 or 2 g/day) and placebo on OA radiographic progression and symptoms[34]. We conducted a *post-hoc* analysis of the placebo arm.

Study design and patients

All details of study design and inclusion criteria were described previously[34,35]. Briefly, the study included Caucasian ambulatory men and women aged ≥50 years with symptomatic and radiographic evidence of knee OA according to American College of Rheumatology criteria[36] and the KL scale[31], respectively. Radiographic inclusion criteria included OA features defined by KL grade 2 [definite osteophytes and possible joint space narrowing (JSN)] or grade 3 (moderate multiple osteophytes, definite JSN, some sclerosis, and possible deformity of bone ends) and JSW of the medial tibiofemoral compartment of 2.5–5 mm. If both knees fulfilled the selection criteria, the target knee was the most painful; if both knees were equally painful, the target knee had the highest KL grade and/or the lowest JSW; and if both knees had the same radiographic score, the target knee was determined by the investigator's judgement. Exclusion criteria were knee prosthesis, recent intra-articular injection (notably glucocorticoids <3 months previously or hyaluronic acid <6 months previously), clinical deformities, secondary knee OA, previous treatments for cartilage or bone metabolism (e.g., oral or intravenous bisphosphonates <1 year previously, teriparatide or raloxifene <7 days before selection, and oral glucosamine ≥1500 mg/day and chondroitin sulphate <3 months previously), and a history or a high risk of venous thromboembolism (contraindication for strontium ranelate).

Baseline examination

The presence or absence of diabetes mellitus, hypertension and dyslipidemia was determined at baseline interview according to medical past history reported by patients. In the design of the study, medical database included only keywords « diabetes mellitus », « type 1 diabetes mellitus » and « type 2 diabetes mellitus ». Thus, the patients with other type of diabetes such as glucocorticoid-induced diabetes or unknown type of diabetes were all included in the group “diabetes mellitus” but not in the subgroups “type 1 diabetes mellitus” or “type 2 diabetes mellitus”. The sum of metabolic factors (obesity, diabetes mellitus, hypertension and dyslipidemia) was calculated. MetS was defined by the sum of metabolic factors ≥3. A history of ischemic disease such as ischemic heart disease, cerebral ischemic disease and peripheral arterial vascular disease was noted. Height and weight were measured and BMI was calculated; obesity was considered >30 kg/m^2.

Other investigations involved the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and global knee pain [visual analog scale (VAS)] at inclusion. WOMAC evaluates OA health status and outcomes with 24 questions[37] summarized as a total score and pain, stiffness and physical function subscores. For each question, we used a 100-mm scale, with a maximal score of 2400 mm for the total score, 500 mm for pain, 200 mm for stiffness, and 1700 mm for physical function, lower scores indicating better status.

Radiographic assessment

Posteroanterior knee radiographs were performed on both knees at inclusion and then annually on the target knee alone by use of a standardised technique[38]. A reproductible knee fixed flexion (20°) was achieved using a SynaFlexer positioning frame (Synarc Inc., San Francisco, CA, USA). The X-ray beam was tilted at a fixed angle of 10° to optimise alignment of the medial tibial plateau. Quality control (Synarc Inc., Hamburg) included specifications for image acquisition and collection (e.g., depiction, positioning and beam angle), regular training for radiology technicians, determination of radiographic eligibility and onsite and centralised digitisation and quality control of radiographs[35].

Minimal JSW (mm) at the medial tibiofemoral compartment was measured by a standardised computer-assisted method[35,39]. Briefly, magnification was determined (radio-opaque ruler) and a region of interest was delimited by a horizontal tangent to the inferior edges of each femoral condyle and two perpendiculars to the condylar margins. Within an area defined automatically by two parallel lines 15 mm apart (with one 10 mm from the condyle line), the observer delineated the tibial and femoral bone margins to depict a polygon; JSW was the diameter of the smallest circle (automatically calculated) in this polygon.

All radiographs were measured centrally (INSERM UMR 1033, Lyon, France) by a single reader blinded to treatment allocation and patient identity. Each blinded post-baseline image was measured in comparison with the inclusion image to optimise reproducibility and sensitivity[40–42]. Intrareader reproducibility was evaluated yearly with 70 knee radiographs unlinked to the study; reproducibility was satisfactory (intraclass correlation coefficient for JSW >0.90)[40]. Annualised JSN was calculated as the ratio of total JSN over the study duration to number of years until exit from or the end of the study.

Statistical analysis

Baseline characteristics are presented as number (%) or mean ± SD. Annualised JSN values and WOMAC scores are

presented as mean (SD) and median (quartile 1, quartile 3), respectively. A t test was used to assess the association of each metabolic or clinical factor and annualised JSN. The association of the sum of metabolic factors was assessed by one-way ANOVA. We used a multivariate linear regression analysis to adjust for age, sex, BMI and each metabolic factor. The effect of metabolic factors on WOMAC scores was studied by a Mann–Whitney test. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of the placebo group

In total, 559 patients were randomly allocated to the placebo group of the SEKOIA trial; 87 were excluded from the intent-to-treat (ITT) analysis because of lack of data on baseline evaluation ($n = 1$), post-baseline evaluation ($n = 87$) or treatment ($n = 3$). Among all placebo patients, 392 (70%) were women and the mean age was 62.8 [62.2–63.4] years. The mean BMI was 29.8 [29.4–30.2] kg/m^2 and 245 patients (43.8%) were obese. 51 patients (9.1%) had diabetes mellitus, which was specified as a type 2 diabetes mellitus in 37 patients (6.6%) and a type 1 diabetes mellitus in one patient (0.2%). 252 (45.1%) had hypertension, 154 (27.6%) had dyslipidemia, and 76 (13.6%) had MetS (Table I). Moreover, 75 patients (13.4%) had a history of ischemic disease.

On 559 target knees, 551 were selected because more painful or with higher KL grade and/or lower JSW while only 8 (1.43%) were determined by the investigator's judgement. At baseline, mean knee pain assessed by VAS was 53.7 [51.8–55.6] mm and mean WOMAC scores were 998.5 [955.7–1041.3], 211.2 [202.2–220.2], 91.1 [86.9–95.3] and 694.7 [663.0–726.4] for total score and pain, stiffness and physical function, respectively. Radiological staging showed that 350 patients (63%) had a KL grade 2 and 209 (37%) a KL grade 3. Mean JSW at the medial femorotibial compartment was 3.51 [3.44–3.58] mm at baseline (Table I). There was no significant difference in the JSW at baseline depending on the presence of each metabolic factor or their accumulation.

Role of diabetes in knee OA progression in the ITT sample of the placebo arm

The mean annualised JSN was greater in patients with type 2 diabetes than those without diabetes (−0.26 [−0.35 to −0.17] vs −0.14 [−0.16 to −0.12] mm; $P = 0.001$) (Table II). Multivariate analysis adjusting for age, sex, BMI, hypertension and dyslipidemia confirmed the independent role of type 2 diabetes ($\beta = -0.12$ [−0.22 to −0.02], P-value = 0.018) (data not shown). In subgroup analysis, the association between type 2 diabetes and annualised JSN was found in males (−0.38 [−0.57 to −0.19] vs −0.16

Table I
Demographic data for patients with knee OA in the placebo group of the SEKOIA trial

	All patients ($n = 559$)	Males ($n = 167$)	Females ($n = 392$)
Age (years)	62.8 [62.2–63.4]	63.8 [62.6–65.0]	62.3 [61.6–63.0]
Weight (kg)	80.8 [79.5–82.1]	90.8 [88.7–92.9]	76.5 [75.0–78.0]
Height (cm)	164.6 [163.8–165.4]	174.7 [173.5–175.9]	160.3 [159.6–161.0]
BMI (kg/m^2)	29.8 [29.4–30.2]	29.8 [29.2–30.4]	29.8 [29.3–30.3]
Obesity (BMI > 30 kg/m^2)	245 (43.8%)	67 (40.1%)	178 (45.4%)
Smoking			
No	359 (64%)	79 (47%)	280 (71%)
Past user	142 (25%)	67 (40%)	75 (19%)
Current user	58 (10%)	21 (13%)	37 (9%)
Alcohol consumption			
No	284 (51%)	39 (23%)	245 (63%)
Past user	8 (1%)	4 (2%)	4 (1%)
Current user	267 (48%)	124 (74%)	143 (36%)
Disease duration (months)	74.8 [68.5–81.1]	88.7 [75.1–102.3]	68.9 [62.1–75.7]
Kellgren–Lawrence grade			
Grade 2	350 (63%)	103 (62%)	247 (63%)
Grade 3	209 (37%)	64 (38%)	145 (37%)
Knee JSW at baseline (mm)	3.51 [3.44–3.58]	3.65 [3.53–3.77]	3.45 [3.37–3.53]
Knee pain VAS (0–100 mm)	53.7 [51.8–55.6]	48.4 [44.9–51.9]	56.1 [53.8–58.4]
WOMAC score*			
Total (/2400 mm)	998.5 [955.7–1041.3]	899.2 [820.1–970.3]	1040.4 [990.1–1090.7]
Pain (/500 mm)	211.2 [202.2–220.2]	194.9 [178.8–211.0]	218.1 [207.3–228.9]
Stiffness (/200 mm)	91.1 [86.9–95.3]	83.2 [75.9–90.5]	94.4 [89.3–99.5]
Physical function (/1700 mm)	694.7 [663.0–726.4]	618.3 [559.9–676.7]	727.4 [690.1–764.7]
Physical assessment at baseline			
Swelling	104 (18.7%)	30 (18.1%)	74 (18.9%)
Warmth	22 (3.9%)	8 (4.8%)	14 (3.6%)
Effusion	72 (12.9%)	27 (16.3%)	45 (11.5%)
Diabetes mellitus†	51 (9.1%)	17 (10.2%)	34 (8.7%)
Type 1	1 (0.2%)	1 (0.6%)	0 (0.0%)
Type 2	37 (6.6%)	14 (8.4%)	23 (5.9%)
Hypertension	252 (45.1%)	73 (43.7%)	179 (45.7%)
Dyslipidemia	154 (27.6%)	51 (30.5%)	103 (26.3%)
Metabolic syndrome‡	76 (13.6%)	23 (13.8%)	53 (13.5%)
Ischemic diseases	75 (13.4%)	36 (21.6%)	39 (10.0%)
Ischemic heart disease	60 (10.8%)	30 (18.0%)	30 (7.7%)
Ischemic cerebral disease	11 (2.0%)	4 (2.4%)	7 (1.8%)
Peripheral arterial disease	4 (0.7%)	2 (1.2%)	2 (0.5%)

Data are number of patients (%) or mean [95%CI].
* Each WOMAC item is measured on a 100-mm scale.
† "Diabetes mellitus" subset includes all patients reporting diabetes mellitus at baseline;
‡ Metabolic syndrome is defined by the sum of metabolic factors ≥3.

Table II
Univariate analyse of knee OA progression by metabolic factors and ischemic diseases in the intent-to-treat population of the placebo arm of the SEKOIA trial

	Annualised JSN (mm)		
	All patients ($n = 472$)	Males ($n = 146$)	Females ($n = 326$)
Obesity (BMI $\geq$ 30 kg/m^2)			
No	−0.15 [−0.18 to −0.12] ($n = 269$)	−0.18 [−0.25 to −0.11] ($n = 89$)	−0.13 [−0.16 to −0.10] ($n = 180$)
Yes	−0.15 [−0.19 − to 0.11] ($n = 203$)	−0.16 [−0.23 to 0.09] ($n = 57$)	−0.14 [−0.18 to −0.10] ($n = 146$)
P-value	0.988	0.672	0.615
Diabetes mellitus*			
No	−0.14 [−0.16 to −0.12] ($n = 430$)	−0.16 [−0.21 to −0.11] ($n = 132$)	−0.13 [−0.16 to −0.10] ($n = 298$)
Yes	−0.21 [−0.29 to −0.13] ($n = 42$)	−0.35 [−0.52 to −0.18] ($n = 14$)	−0.14 [−0.20 to −0.08] ($n = 28$)
P-value	0.093	0.027	0.831
Diabetes type 2			
No	−0.14 [−0.16 to −0.12] ($n = 443$)	−0.16 [−0.21 to −0.11] ($n = 134$)	−0.13 [−0.16 to −0.10] ($n = 309$)
Yes	−0.26 [−0.35 to −0.17] ($n = 29$)	−0.38 [−0.57 to −0.19] ($n = 12$)	−0.19 [−0.28 to −0.10] ($n = 17$)
P-value	0.001	0.016	0.333
Hypertension			
No	−0.14 [−0.17 to −0.11] ($n = 260$)	−0.17 [−0.23 to −0.11] ($n = 85$)	−0.12 [−0.15 to −0.09] ($n = 175$)
Yes	−0.15 [−0.19 to −0.11] ($n = 212$)	−0.19 [−0.28 to −0.10] ($n = 61$)	−0.14 [−0.18 to −0.10] ($n = 151$)
P-value	0.494	0.663	0.533
Dyslipidemia			
No	−0.14 [−0.17 to −0.11] ($n = 342$)	−0.19 [−0.25 to −0.13] ($n = 103$)	−0.13 [−0.16 to −0.10] ($n = 239$)
Yes	−0.15 [−0.19 to −0.11] ($n = 130$)	−0.15 [−0.22 to −0.08] ($n = 43$)	−0.15 [−0.20 to −0.10] ($n = 87$)
P-value	0.765	0.544	0.379
Sum of metabolic factors			
0	−0.13 [−0.17 to −0.09] ($n = 147$)	−0.16 [−0.24 to −0.08] ($n = 48$)	−0.12 [−0.17 to −0.07] ($n = 99$)
1	−0.14 [−0.18 to −0.10] ($n = 142$)	−0.19 [−0.29 to −0.09] ($n = 45$)	−0.12 [−0.16 to −0.08] ($n = 97$)
2	−0.15 [−0.20 to −0.10] ($n = 118$)	−0.17 [−0.27 to −0.07] ($n = 33$)	−0.15 [−0.21 to −0.09] ($n = 85$)
3	−0.17 [−0.24 to −0.10] ($n = 51$)	−0.20 [−0.36 to −0.04] ($n = 16$)	−0.16 [−0.23 to −0.09] ($n = 35$)
4	−0.15 [−0.25 to −0.05] ($n = 14$)	−0.17 [−0.39 to 0.05] ($n = 4$)	−0.14 [−0.26 to −0.02] ($n = 10$)
P-value	0.918	0.980	0.882
Metabolic Syndrome†			
No	−0.14 [−0.17 to −0.11] ($n = 407$)	−0.17 [−0.22 to −0.12] ($n = 126$)	−0.13 [−0.16 to −0.10] ($n = 281$)
Yes	−0.17 [−0.23 to −0.11] ($n = 65$)	−0.20 [−0.33 to −0.07] ($n = 20$)	−0.15 [−0.21 to −0.09] ($n = 45$)
P-Value	0.503	0.731	0.555
Ischemic diseases			
Ischemic heart disease			
No	−0.14 [−0.16 to −0.12] ($n = 421$)	−0.19 [−0.24 to −0.14] ($n = 123$)	−0.12 [−0.15 to −0.09] ($n = 298$)
Yes	−0.17 [−0.25 to −0.09] ($n = 51$)	−0.12 [−0.23 to −0.01] ($n = 23$)	−0.21 [−0.32 to −0.10] ($n = 28$)
P-value	0.433	0.379	0.060
Ischemic cerebral disease			
No	−0.15 [−0.17 to −0.13] ($n = 462$)	−0.18 [−0.23 to −0.13] ($n = 142$)	−0.13 [−0.16 to −0.10] ($n = 320$)
Yes	−0.10 [−0.21 to 0.01] ($n = 10$)	−0.04 [−0.21 to 0.13] ($n = 4$)	−0.13 [−0.28 to 0.02] ($n = 6$)
P-value	0.540	0.362	0.983
Peripheral arterial disease			
No	−0.15 [−0.17 to −0.13] ($n = 469$)	−0.18 [−0.23 to −0.13] ($n = 145$)	−0.13 [−0.16 to −0.10] ($n = 324$)
Yes	0.01 [−0.16 to 0.18] ($n = 3$)	0.2 ($n = 1$)	−0.08 [−0.09 to −0.07] ($n = 2$)
P-value	0.293	–	0.729

Data are mean [95% CI] (n) change in joint space per year.
* "Diabetes mellitus" subset includes all patients reporting diabetes mellitus at baseline.
† Metabolic syndrome is defined by the sum of metabolic factors ≥3.

[−0.21 to −0.11] mm, $P = 0.016$) but not females (−0.19 [−0.28 to −0.10] vs −0.13 [−0.16 to −0.10] mm, $P = 0.333$) (Table II).

Obesity, hypertension and dyslipidemia had no impact on annualised JSN (−0.15 [−0.19 to −0.11] vs −0.15 [−0.18 to −0.12] mm, $P = 0.988$; −0.15 [−0.19 to −0.11] vs −0.14 [−0.17 to −0.11] mm, $P = 0.494$ and −0.15 [−0.19 to −0.11] vs −0.14 [−0.17 to −0.11] mm, $P = 0.765$, respectively) (Table II). Similar results were found for males and females. Moreover, we found neither cumulative effect of metabolic factors on knee OA progression (all patients: $P = 0.918$, males: $P = 0.980$ and females: $P = 0.882$) nor association between MetS and annualised JSN (all patients: −0.17 [−0.23 to −0.11] vs −0.14 [−0.17 to −0.11] mm, $P = 0.503$, males: −0.20 [−0.33 to −0.07] vs −0.17 [−0.22 to −0.12] mm, $P = 0.731$ and females: −0.15 [−0.21 to −0.09] vs −0.13 [−0.16 to −0.10] mm, $P = 0.555$) (Table II). Arteriosclerotic vascular diseases including ischemic heart disease, ischemic cerebral disease and peripheral arterial disease did not seem to be involved in knee OA progression, although we found a trend towards a positive association between ischemic heart disease and annualised JSN in females (−0.21 [−0.32 to −0.10] vs −0.12 [−0.15 to −0.09] mm, $P = 0.060$) (Table II).

Impact of metabolic factors on pain and function at baseline

Among metabolic factors, obesity was the sole factor associated with worsening pain, stiffness and physical function score (241 vs 177, $P < 0.0001$; 106 vs 81, $P = 0.0003$ and 809 vs 557, $P < 0.0001$), respectively) (Table III). Almost all WOMAC subscores were higher but not significantly in the presence of one of the metabolic factors, except for the stiffness subscore in patients with hypertension and type 2 diabetes (Table III). Similarly, MetS was not significantly associated with worsening WOMAC subscores (288 vs 199, $P = 0.243$ for pain score; 101.5 vs 94, $P = 0.691$ for stiffness score and 758.9 vs 645.5, $P = 0.241$ for function score) (Table III). We found no association between WOMAC subscores and ischemic diseases, except for ischemic cerebral disease significantly associated with stiffness and physical function subscores (124 vs 94, $P = 0.032$ and 881 vs 658, $P = 0.040$, respectively) (Table III).

Table III
Involvement of metabolic factors in symptoms of knee OA by WOMAC subscores at baseline

	WOMAC Pain score (/500 mm) ($n = 551$)	WOMAC stiffness (/200 mm) ($n = 557$)	WOMAC physical function score (/1700 mm) ($n = 554$)
Obesity (BMI $\geq$ 30 kg/m^2)			
No	177 (113; 262) ($n = 308$)	81 (44; 123) ($n = 312$)	557 (310; 864) ($n = 311$)
Yes	241 (159; 326) ($n = 243$)	106 (60; 137) ($n = 245$)	809 (540; 1137) ($n = 243$)
P-value	<0.0001	0.0003	<0.0001
Diabetes mellitus*			
No	200 (122; 288) ($n = 500$)	95 (49; 132) ($n = 506$)	653 (387; 973) ($n = 503$)
Yes	226 (147; 291) ($n = 51$)	101 (54; 121) ($n = 51$)	751 (391; 1028) ($n = 51$)
P-value	0.407	0.872	0.615
Diabetes type 2			
No	201 (122; 287) ($n = 514$)	97 (50; 131) ($n = 520$)	658 (393; 976) ($n = 517$)
Yes	220 (164; 286) ($n = 37$)	93 (54; 123) ($n = 37$)	712 (387; 886) ($n = 37$)
P-value	0.656	0.995	0.909
Hypertension			
No	200 (116; 277) ($n = 303$)	98 (48; 133) ($n = 305$)	613 (361; 949) ($n = 303$)
Yes	209 (136; 291) ($n = 248$)	95 (53; 123) ($n = 252$)	731 (418; 1002) ($n = 251$)
P-value	0.195	0.927	0.082
Dyslipidemia			
No	192 (121; 281) ($n = 400$)	91 (47; 132) ($n = 403$)	638 (378; 949) ($n = 401$)
Yes	226 (138; 294) ($n = 151$)	102 (61; 124) ($n = 154$)	725 (410; 1020) ($n = 153$)
P-value	0.059	0.382	0.128
Metabolic Syndrome†			
No	199 (122; 287) ($n = 475$)	94 (49; 132) ($n = 481$)	645.5 (381; 952) ($n = 478$)
Yes	288 (153; 291) ($n = 76$)	101.5 (58; 120.5) ($n = 76$)	758.9 (414; 1017) ($n = 76$)
P-value	0.243	0.691	0.241
Ischemic diseases			
Ischemic heart disease			
No	200 (122; 288) ($n = 493$)	96 (50; 132) ($n = 498$)	649 (383; 949) ($n = 494$)
Yes	231 (138; 274) ($n = 58$)	99 (51; 123) ($n = 59$)	796 (485; 1023) ($n = 60$)
P-value	0.344	0.957	0.084
Ischemic cerebral disease			
No	201 (122; 288) ($n = 540$)	94 (49; 130) ($n = 546$)	658 (384; 973) ($n = 543$)
Yes	237 (184; 299) ($n = 11$)	124 (95; 154) ($n = 11$)	881 (770; 1070) ($n = 11$)
P-value	0.203	0.032	0.040
Peripheral arterial disease			
No	203 (125; 288) ($n = 548$)	97 (50; 130) ($n = 553$)	668 (392; 973) ($n = 550$)
Yes	58 (49; 239) ($n = 3$)	45 (9; 109) ($n = 4$)	574 (104; 1045) ($n = 4$)
P-value	0.123	0.227	0.549

Data are median (quartile 1; quartile 3).
* "Diabetes mellitus" subset includes all patients reporting diabetes mellitus at baseline.
† Metabolic syndrome is defined by the sum of metabolic factors $\geq$3.

Discussion

Our study is the first to evaluate the link between metabolic factors and radiographic progression of knee OA based on an annual accurate measure of JSN. We showed that type 2 diabetes was associated with a greater radiographic progression in males. The only other study evaluating radiographic knee OA progression also highlighted the potential effect of diabetes on disease progression[28]: knee OA patients with hemoglobin A1c $\geq$5.5% had a greater risk of disease progression over 3 years ($P = 0.029$) after adjustment for age and sex. However, this association disappeared after adjustment for other OA risk factors and others components of the MetS.

How diabetes might interfere with the OA disease process? Hyperglycemia may lead to glycation of cartilage resident proteins especially those exhibiting low turnover such as type II collagen[43]. By changing their physical properties, this glycation could increase the stiffness of cartilage collagen network and so reduce its resistance to mechanical stress[44]. Moreover, several recent studies highlighted a central role of advanced glycation end products (AGE) and their receptors (RAGE) in the inflammatory and degradative process in OA. AGE enhanced the production of interleukin 6 and matrix metalloproteinase (MMP)-13 and the expression of cyclooxygenase 2 and reduced that of collagen II in human OA chondrocytes[45]. Steenvoorden *et al.* showed a catabolic effect on human OA synoviocytes induced by glycated albumin, with an increase in MMP-1 production and catabolic activity[46]. Otherwise, the association between diabetes and knee OA could also involve the production of reactive oxygen species (ROS) by OA chondrocytes, which is increased in response to prolonged hyperglycemia and known to induce degradation of cartilage matrix proteins[47].

The specific link between knee OA and diabetes in males had already been suggested in a previous study[27]. Indeed, in obese subjects, knee OA prevalence was associated with insulin resistance only in males [OR = 1.34 (1.27–1.42) in males and OR = 0.88 (0.86–0.89) in females]. However, we have no clear explanation of this specific association, although both basic and clinical studies may provide some explanation. Selvin *et al.* recently showed that male sex was associated with a lower level of soluble RAGE (sRAGE), which are suspected to partially counteract the pro-inflammatory effect of AGE by decreasing their binding on RAGE[48]. However, this hypothesis remains controversial, given the very low level of sRAGE as compared with circulating AGE[49,50]. Another explanation could be provided by the gender specifities of diabetic complications[51–56]. Indeed, distal neuropathy seems to occur more frequently and earlier in diabetic men as compared with diabetic women[52,55,56]. Furthermore, a recent study showed diabetic polyneuropathy was associated with increased rate of bone turnover in males assessed by different biomarkers (e.g., C-terminal telopeptide 1, propeptide of human procollagen type I, osteocalcin)[53].

Consequently, greater knee OA progression in diabetic men could be due in part to indirect consequences of neuropathy both on pain sensitivity compromising the joint saving[57] and on metabolism of tissues such as bone implicated in the OA pathophysiology[53]. Unfortunately, we lack this kind of information in the baseline demographic data in SEKOIA trial.

Obesity was not associated with disease progression over the study duration. This result seems all the more surprising since there was a strong association between weight status and the severity of clinical symptoms at baseline, which had already been identified as linked with radiological progression[58,59]. Thus, we may expect that obese patient who were the most painful, had a profile of a more rapid radiological progression. However, pain intensity could be considered as a confounding factor, more reflecting the extension of joint damage (such as bone edema or rapid chondrolysis) rather than directly influencing knee OA progression. Moreover, clinical symptoms were collected at baseline and did not necessarily reflect the level of pain throughout the study. Moreover, as only 17.2% of patients had a normal weight (<25 kg/m^2), it was methodologically difficult to realize any valid comparison between obese (BMI $\geq$ 30 kg/m^2) or overweight patients (25 kg/m^2 < BMI < 30 kg/m^2) and normal patients (BMI < 25 kg/m^2) and so we only compared obese patients to others, having either normal BMI or more frequently overweight, which could hide the effect of obesity on radiological progression. Actually, although obesity is considered a key factor of knee OA progression, a detailed review of the literature provided conflicting data: long-term follow-up studies indicated that obesity is a strong risk factor for knee OA progression[60–62], but other studies with a shorter follow-up provided opposite results, showing no robust association[5,63,64]. Similarly, in our study, the short follow-up could be insufficient to observe an effect of overweight, especially because most patients had a BMI >25 kg/m^2. Otherwise, these conflicting results may be linked to differences in the "phenotype" of knee OA. Several studies highlighted a crucial effect of the association of misalignment plus obesity on knee OA progression[63,65,66]. In the SEKOIA trial, excluding patients with significant misalignment could explain the lack of effect of obesity on knee OA progression.

Like obesity, dyslipidemia and hypertension did not seem to affect radiographic progression of knee OA. However, Yoshimura *et al.* showed hypertension, defined as systolic blood pressure >130 mm Hg and/or diastolic blood pressure >85 mm Hg or medication intake, as a risk factor of disease progression (RR = 1.54) even after adjustment for BMI and other metabolic factors[28]. Unlike Yoshimura *et al.*, we did not find any cumulative effect of metabolic factors on radiographic progression over 3 years, which is consistent with our results showing a unique role of diabetes.

Concerning the clinical symptoms, obesity was the sole metabolic factor significantly associated with pain, stiffness and function assessed by WOMAC scores. Unlike Schett *et al.*[30], we found no association of diabetes and symptom severity in our study.

Our study presents some limitations. First of all, this was a *post-hoc* analysis, not included in the initial design of the SEKOIA trial. Furthermore, the definition of metabolic factors in SEKOIA was based solely on medical history without blood pressure measurement or a blood test to measure lipid and glucose. Consequently, we selected patients with advanced or well-recognized diseases (at least by the patient himself), but may ignore those with unrecognized or silent metabolic diseases; this could induce an information bias by misclassification. This bias seems to be confirmed by the prevalence of metabolic factors (except for obesity) and the SM noted in our study, which are lower than those found in a French population of the same age[67]. Consequently, further studies need to include validated criteria defined by experts for each metabolic factor[17]. Finally, several factors, which may be related to disease progression of knee OA were not recorded at baseline, such as bone mass[68] but also physical activity[69].

Our study also has several strengths. First, we used the placebo arm of a controlled, multicentre study allowing a rigorous data collection. Overall, this is the first study, which evaluates the involvement of metabolic factors in radiographic progression of knee OA using a reliable and reproducible measurement of JSW rather than the KL grade, which is less accurate, less sensitive to change and a source of great variability in interpretation.

To conclude, among metabolic factors, only diabetes appeared to be a strong factor associated with radiographic progression of knee OA in males. These results might open a new therapeutic avenue in terms of prevention of disease progression with a special focus on glycemic equilibrium. We did not study the impact of glycemic control on disease progression since glycemia was not measured in the SEKOIA trial. However, this hypothesis seems plausible as it has been shown that a tight glycemic control could reduce the rate of circulating or tissular AGE[70,71] in addition to decrease the blood glucose, which are potentially involved in OA pathophysiology[45–47]. Finally, further longitudinal studies including type 1 diabetes would be of interest in order to assess the specific impact of chronic hyperglycemia (e.g., protein glycation) on OA progression as there will be less confounding « pro-inflammatory factors » such as those found in type 2 diabetes (obesity, dyslipidemia or hypertension). However, as type 1 diabetes is a much rarer disease than type 2 diabetes, it is more difficult to form large homogeneous cohorts with a long-term follow-up.

Contributorship statement

FE and CP contributed to the design of the study, the analysis and interpretation of data. They wrote the manuscript. They contributed equally to the work.

ME contributed to the design of the study, the analysis and interpretation of data. He participated substantially to the reviewing of the manuscript before submission.

FPD, JYR and OB contributed to the interpretation of data. They participated substantially to the reviewing of the manuscript before submission.

PR contributed to the design of the study and the interpretation of data. He participated substantially to the reviewing of the manuscript before submission.

CC and XC contributed to the conception of the study and the interpretation of data. They participated substantially to the reviewing and editing of the manuscript before submission. They contributed equally to the work.

All authors approved the version submitted.

Ethical approval information

SEKOIA trial was approved by the ethics committee or institutional review board of every centre.

Funding

No external funding was received for this study.

Competing interests

- FPD is Servier employee.
- JYR has received consulting fees, lecture fees, and/or grant support from Servier, Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk, Nolver, Negma, Wyeth, Amgen,

Merckle, NPS, UCB, Bristol Myers Squibb and Merck Sharp & Dohme.
- OB has received consulting fees, lecture fees, grant support and/or reimbursement for attending meeting from Servier, IBSA, Merck Sharp & Dohme, Novartis, Nutraveris, Pfizer, Rottapharm, SMB, Bayer, Genevrier and Theramex.
- PR has received fees from Servier, Sanofi, Genzyme, Expanscience, Genevrier, Pfizer, Abbot, Ibsa, Biolbérica, Fidia.
- CC has received consultancy, lecture fees and honoraria from AMGEN, GSK, Alliance for Better Bone Health, MSD, Eli Lilly, Pfizer, Novartis, Servier, Merck, Medtronic and Roche.
- XC has received fees from Servier, Expanscience, Flexion therapics, Moebius, Sanofi, Genevrier, Pierre Fabre, Nordic Pharma and IBSA.
- Other authors (FE, CP and ME) have no competing interests.

Acknowledgments

We are grateful to SERVIER for allowing us to use the database of SEKOIA trial.

References

1. Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartilage 2011;19:1270–85.
2. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, *et al*. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133:635–46.
3. Picavet HSJ, Hazes JMW. Prevalence of self reported musculoskeletal diseases is high. Ann Rheum Dis 2003;62:644–50.
4. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.
5. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, *et al*. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
6. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 2014;73:1659–64.
7. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, *et al*. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.
8. Suri P, Morgenroth DC, Hunter DJ. Epidemiology of osteoarthritis and associated comorbidities. PM R 2012;4:S10–9.
9. Yusuf E, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G, *et al*. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010;69:761–5.
10. Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, Jacobson JA, Jiang Y, Ashton-Miller JA. Knee osteoarthritis in obese women with cardiometabolic clustering. Arthritis Rheum 2009;61:1328–36.
11. Lawrence JS. Hypertension in relation to musculoskeletal disorders. Ann Rheum Dis 1975;34:451–6.
12. Stürmer T, Sun Y, Sauerland S, Zeissig I, Günther KP, Puhl W, *et al*. Serum cholesterol and osteoarthritis. The baseline examination of the Ulm Osteoarthritis Study. J Rheumatol 1998;25:1827–32.
13. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.
14. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiological survey. Clin Exp Rheumatol 1990;8:251–7.
15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
16. Alberti KGMM, Zimmet P, Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome–a new worldwide definition. Lancet 2005;366:1059–62.
17. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
18. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415–28.
19. Libby P. Inflammation in atherosclerosis. Nature 2002;420:868–74.
20. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012;32:2045–51.
21. Festa A, D'Agostino Jr R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–7.
22. Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford, England) 2005;44:7–16.
23. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol 2013;25:114–8.
24. Inoue R, Ishibashi Y, Tsuda E, Yamamoto Y, Matsuzaka M, Takahashi I, *et al*. Medical problems and risk factors of metabolic syndrome among radiographic knee osteoarthritis patients in the Japanese general population. J Orthop Sci 2011;16:704–9.
25. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9–20.
26. Han CD, Yang IH, Lee WS, Park YJ, Park KK. Correlation between metabolic syndrome and knee osteoarthritis: data from the Korean National Health and Nutrition Examination Survey (KNHANES). BMC Public Health 2013;13:603.
27. Karvonen-Gutierrez CA, Sowers MR, Heeringa SG. Sex dimorphism in the association of cardiometabolic characteristics and osteophytes-defined radiographic knee osteoarthritis among obese and non-obese adults: NHANES III. Osteoarthritis Cartilage 2012 Jul;20(7):614–21.
28. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, *et al*. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage 2012;20:1217–26.
29. Monira Hussain S, Wang Y, Cicuttini FM, Simpson JA, Giles GG, Graves S, *et al*. Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. Semin Arthritis Rheum 2014;43:429–36.
30. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, *et al*. Diabetes is an independent predictor for

severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403–9.
31. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
32. Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis 2011;70:1884–6.
33. Ornetti P, Brandt K, Hellio-Le Graverand M-P, Hochberg M, Hunter DJ, Kloppenburg M, *et al*. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. Osteoarthritis Cartilage 2009;17:856–63.
34. Reginster J-Y, Badurski J, Bellamy N, Bensen W, Chapurlat R, Chevalier X, *et al*. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis 2013;72:179–86.
35. Cooper C, Reginster J-Y, Chapurlat R, Christiansen C, Genant H, Bellamy N, *et al*. Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. Curr Med Res Opin 2012;28:231–9.
36. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
37. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
38. Kothari M, Guermazi A, von Ingersleben G, Miaux Y, Sieffert M, Block JE, *et al*. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. Eur Radiol 2004;14:1568–73.
39. Gensburger D, Arlot M, Sornay-Rendu E, Roux J-P, Delmas P. Radiologic assessment of age-related knee joint space changes in women: a 4-year longitudinal study. Arthritis Rheum 2009;61:336–43.
40. Gensburger D, Roux J-P, Arlot M, Sornay-Rendu E, Ravaud P, Chapurlat R. Influence of blinding sequence of radiographs on the reproducibility and sensitivity to change of joint space width measurement in knee osteoarthritis. Arthritis Care Res 2010;62:1699–705.
41. Botha-Scheepers S, Watt I, Breedveld FC, Kloppenburg M. Reading radiographs in pairs or in chronological order influences radiological progression in osteoarthritis. Rheumatology 2005;44:1452–5.
42. Felson DT, Nevitt MC. Blinding images to sequence in osteoarthritis: evidence from other diseases. Osteoarthritis Cartilage 2009;17:281–3.
43. Eyre DR, Weis MA, Wu J-J. Articular cartilage collagen: an irreplaceable framework? Eur Cell Mater 2006;12:57–63.
44. Verzijl N, DeGroot J, Ben ZC, Brau-Benjamin O, Maroudas A, Bank RA, *et al*. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possible mechanism through which age is a risk factor for osteoarthritis. Arthritis Rheum 2002;46:114–23.
45. Chen YJ, Sheu ML, Tsai KS, Yang RS, Liu SH. Advanced glycation end products induce peroxisome proliferator-activated receptor γ down-regulation-related inflammatory signals in human chondrocytes via Toll-like receptor-4 and receptor for advanced glycation end products. PloS One 2013;8:e66611.
46. Steenvoorden MMC, Huizinga TWJ, Verzijl N, Bank RA, Ronday HK, Luning HAF, *et al*. Activation of receptor for advanced glycation end products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. Arthritis Rheum 2006;54:253–63.
47. Rosa SC, Gonçalves J, Judas F, Mobasheri A, Lopes C, Mendes AF. Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in chondrocytes from osteoarthritic versus normal human cartilage. Arthritis Res Ther 2009;11:R80.
48. Selvin E, Halushka MK, Rawlings AM, Hoogeveen RC, Ballantyne CM, Coresh J, *et al*. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116–21.
49. Schalkwijk CG, Stehouwer CDA. Comment on: Selvin et al. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116–2121. Diabetes 2013;62:e25.
50. Yamagishi S. Comment on: Selvin et al. sRAGE and risk of diabetes, cardiovascular disease, and death. Diabetes 2013;62:2116–2121. Diabetes 2013;62:e26.
51. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, *et al*. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. J Intern Med 2013;274:176–91.
52. Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). The DCCT Research Group. Diabetes 1988;37:476–81.
53. Rasul S, Ilhan A, Wagner L, Luger A, Kautzky-Willer A. Diabetic polyneuropathy relates to bone metabolism and markers of bone turnover in elderly patients with type 2 diabetes: greater effects in male patients. Gend Med 2012;9:187–96.
54. Bruun C, Siersma V, Guassora AD, Holstein P, de Fine Olivarius N. Amputations and foot ulcers in patients newly diagnosed with type 2 diabetes mellitus and observed for 19 years. The role of age, gender and co-morbidity. Diabet Med 2013;30:964–72.
55. Aaberg ML, Burch DM, Hud ZR, Zacharias MP. Gender differences in the onset of diabetic neuropathy. J Diabetes Complicat 2008;22:83–7.
56. Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. BMC Neurol 2005;5:24.
57. Leaverton PE, Peregoy J, Fahlman L, Sangeorzan E, Barrett Jr JP. Does diabetes hide osteoarthritis pain? Med Hypotheses 2012;78:471–4.
58. Riddle DL, Jiranek WA. Knee osteoarthritis radiographic progression and associations with pain and function prior to knee arthroplasty: a multicenter comparative cohort study. Osteoarthritis Cartilage 2015;23:391–6.
59. Karsdal M, Bihlet A, Byrjalsen I, Alexandersen P, Ladel C, Michaels M, *et al*. OA phenotypes, rather than disease stage, drive structural progression – identification of structural progressors from 2 phase III randomized clinical studies with symptomatic knee OA. Osteoarthritis Cartilage 2015;23:550–8.
60. Schouten JS, van den Ouweland FA, Valkenburg HA. A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis 1992;51:932–7.
61. Yusuf E, Bijsterbosch J, Slagboom PE, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis. Osteoarthritis Cartilage 2011;19:1117–22.
62. Reijman M, Pols HAP, Bergink AP, Hazes JMW, Belo JN, Lievense AM, *et al*. Body mass index associated with onset and

progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 2007;66:158–62.
63. Niu J, Zhang YQ, Torner J, Nevitt M, Lewis CE, Aliabadi P, *et al*. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum 2009;61:329–35.
64. Le Graverand M-PH, Brandt K, Mazzuca SA, Raunig D, Vignon E. Progressive increase in body mass index is not associated with a progressive increase in joint space narrowing in obese women with osteoarthritis of the knee. Ann Rheum Dis 2009;68:1734–8.
65. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum 2004;50:3904–9.
66. Brouwer GM, van Tol AW, Bergink AP, Belo JN, Bernsen RMD, Reijman M, *et al*. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis Rheum 2007;56:1204–11.
67. Balkau B, Vernay M, Mhamdi L, Novak M, Arondel D, Vol S, *et al*. The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. Diabetes Metab 2003;29:526–32.
68. Herrero-Beaumont G, Roman-Blas JA, Largo R, Berenbaum F, Castañeda S. Bone mineral density and joint cartilage: four clinical settings of a complex relationship in osteoarthritis. Ann Rheum Dis 2011;70:1523–5.
69. Lin W, Alizai H, Joseph GB, Srikhum W, Nevitt MC, Lynch JA, *et al*. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2013;21:1558–66.
70. Chiarelli F, de Martino M, Mezzetti A, Catino M, Morgese G, Cuccurullo F, *et al*. Advanced glycation end products in children and adolescents with diabetes: relation to glycemic control and early microvascular complications. J Pediatr 1999;134:486–91.
71. Beisswenger PJ, Moore LL, Curphey TJ. Relationship between glycemic control and collagen-linked advanced glycosylation end products in type I diabetes. Diabetes Care 1993;16:689–94.